REMARKS

The Office Action has allowed Claims 23-28, 31, 32, 78-81 and 88-93. However, it has rejected Claims 12-17, 21-22, 73-77, 82-87 and 94-95 under U.S.C. § 112, first paragraph, for allegedly being non-enabling.

Applicants have amended the claims which when considered with the comments hereinbelow, are deemed to place the present case in condition for allowance.

At the outset, Applicants wish to thank Examiner Gupta for granting a telephone interview on June 27, 2006 to discuss the application and for his helpful comments during the interview.

Applicants have amended Claim 12 to be directed to the use of the compounds herein for providing neuroprotection to a subject "resulting form either brain or spinal cord trauma or stroke". Support for the amendment to Claim 12 is found on Page 11, Lines 17-27 of the instant specification. In addition, Applicants have amended Claim 79 to correct a typographical error. No new matter is added to the application.

At the outset, Applicants respectfully submit that there is a mistake in the rejections of the claims. Claim 95 has been rejected, but it is dependent upon Claim 79, and ultimately dependent upon Claim 23, both of which have been allowed. Therefore, it is respectfully submitted that Claim 95 is allowable.

In its rejection, the Office Action indicated that the specification is enabling for methods for enhancing cognitive function and for neuroprotection from traumatic brain injury. However, the Office Action does not believe that the compounds described in the instant specification provide neuroprotection for neurogenerative diseases, such as Alzheimer's disease and Parkinson's disease.

Applicants disagree, and incorporate by reference the comments in their previous Responses including the one dated November 2, 2005. However, in order to advance prosecution, Applicants have amended Claim 12 to recite that the method of neuroprotection to a subject results from either brain or spinal cord trauma or stroke. As a result, the neuroprotection, as currently claimed, does not include neuroprotection from neurodegenerative diseases, such as Parkinson's disease and Alzheimer's disease. Consequently, the comments of the Office Action respecting neuroprotection from neurodegenerative diseases are not applicable to the claimed subject matter. Thus, the rejection of the claims on these grounds has been rendered moot. Applicants, however, have not abandoned that subject matter, and reserve the right the right to file a continuation application directed thereto.

The Office Action has indicated that the present application showed neuroprotection in traumatic brain injury and in cognitive function. The specification provides ample data on test models accepted by one of ordinary skill in the art which shows that the bicyclic 2,5-diketopiparzines disclosed in the present application are useful in effecting neuroprotection, as currently claimed, in a mammal. For example, attention is directed to the in vitro and in vivo experiments described in Examples 8 and 9 on Pages 84-97 of the present application which show using representative examples that the bicyclic 2,5-diketopiperazines are useful in effecting neuroprotection.

Example 8 tested the effect of the administration of representative compounds, such as Compound 2a in beam walking and spatial learning of mice after being subjected to traumatic injury from the incision in the brain from a micro-processor-controlled pneumatic impactor. More specifically, the mice were given a representative compound of the present invention, namely compounds of Formula 2a. As shown by the data in Fig. 3, mice treated with Compound

2a began to show chronic neurological recovery as demonstrated by beam walking, within 3 days and were performing this task considerably better 2-3 weeks post injury relative to mice who were not given the drug. In fact, as described on page 88 et. seq., mice treated with Compound 2a showed significant improvement in performance of this task than when compared with the controlled mice. Furthermore, as shown by the data and described on Page 89, et. seq., mice treated with the representative compound of the present invention were significantly outperforming controlled mice in the beam-walking experiment. See Figure 3 and text accompanying same. In addition, the mice provided with Compound 2a exhibited significantly greater learning relative to the mice in control group (See Fig 6a and 6b). Moreover, as shown in Fig. 7, injured mice treated with Compound 2a had significantly better reference memory function, relative to untreated injured mice, even within 24 hours after trauma (See Fig. 7). Attention is also directed to Example 9 which demonstrates the ability of representative compounds described in the present application for treating neurotrauma in another test animal, rats. Rats subjected to fluid percussion injury and than treated with representative compounds of the present invention showed improved motor recovery. (See Fig 1 and 2). Thus, Applicants have provided in vivo data showing specific neuroprotection from, inter alia, traumatic brain injury.

The allegations in the application regarding the neuroprotection of the diketopiperazines is supported by additional data.

Attention is also directed to the affidavit of Alan Faden, dated October 15, 1999, which provides in vitro evidence using representative compounds of the present invention that the bicyclic 2,5-diketopiperazines block neuronal cell deaths after insults specifically implicated in spinal cord injury and stroke, namely excitotoxic (glutamate induced) and free radical-induced

injuries. Further, the data show neuroprotective effects using an in vitro mode of ischemia (stroke) oxygen glucose deprivation (See paragraphs 7-12). This data specifically supports the allegations of neuroprotection from, inter alia, stroke and spinal cord injury.

Further, neuroprotective effects were tested using a staurosporine model of apoptotic cell death. As shown by the data in Paragraph 13 therein and the referenced exhibits 4 and 5, the treatment with representative compounds described in the instant application increased survival in the model. Further, attention is directed to Paragraph 14, which is directed to testing the neuroprotection in a traumatic injury model, which is an art accepted model for testing neuroprotective effects of compounds. As shown by the data referenced to in paragraph 14, incubation of cultured cells with a representative compound increased the survival of neuronal cells after traumatic injury. Finally, the neuroprotective effects using a representative compound in the necrotic injury model is described in Paragraph 15 thereof. As described in Paragraph 15 and the referenced data, a representative compound of the present invention improved survival in cultures subject to necrotic insult via maitotoxin.

These results are extremely significant especially since the various pathological mechanisms tested in the experiments described hereinabove have been implicated in causing acute neurodegenerative disorders (i.e., stroke, head injury and spinal cord injury).

Applicants have submitted articles which have been reviewed by experts in the field before publication and support the allegations in the instant specification regarding the claimed subject matter. Attention is directed to the articles by Faden, et al in Journal of Cerebral Blood Flow and Metabolism, 2003, 23, 342-354, which tested the effects of a representative diketopiperazine administered to rats in injury models accepted by the skilled artisan to evaluate the neuroprotective action of drugs. As described in the article, the representative compound

significantly reduced cell death associated with necrosis (maitotoxin), apoptosis (Staurosporine) and mechanical injury in neuronal-glial cocultures. It also showed that rats subjected to lateral fluid percussion – induced TBI and then treated with 1 mg/Kg intravenously with the representative compound disclosed in the present application thirty minutes after trauma showed significantly improved motor recovery and spatial learning compared with rats subjected to vehicle treated controls. Treatment with the representative compound also significantly reduced lesion volumes (shown by MRI) and decreased the number of TUNEL-positive neurons observed in ipsilateral hippocampus. Yet, unlike TRH, which is a known neuroprotectant, it did not alter the mean arterial pressure, body temperature or thyroid stimulating hormone release and did not exhibit analeptic activity. Moreover, unlike TRH, administration of the representative compound did not alter free magnesium concentration or the cellular bioenergetic state. Thus, the article shows that the a representative compound exhibited none of the typical physiologic actions associated with TRH, but possesses neuroprotective actions in vivo and in vitro and attenuates both necrotic and apoptotic cell death.

Faden et al in the Journal of Cerebral Blood Flow and Metabolism, 2003, 23, 355-363, previously submitted, evaluated the effects of treatment with a representative compound in a different animal, mice, subjected to controlled cortical impact brain injury in another model system accepted by one of ordinary skill in the art to the evaluate neuroprotection action of the drug. The treated animals showed significantly enhanced recovery of beam walking and place learning functions compared with controls, in addition to reduced lesion volumes. As demonstrated therein, neuroprotective action was found when the drug was administered initially after thirty minutes, or 1, 4, 8 hours after trauma but not at 24 hours. In another experiment, rats treated with this compound on days 7-10 after injury showed remarkably improved place

learning in comparison with injured controls. Thus, the studies showed the neuroprotective effects of the representative compounds caused by traumatic brain injury.

It is to be noted that these two articles may not present any additional data than that which described in the application or the aforementioned declarations. However, these articles were reviewed by peers and experts in the field. If the data did not show evidence of the neuroprotection of the compound described therein, the peers and experts would have objected to the usage of such description thereof. The fact that they permitted the term neuroprotection therein shows that one of ordinary skill in the art accepts that these model systems test and show the neuroprotective properties of the compounds tested to therein.

Another article in Neuropharmacology 2005, previously submitted is in press but which has been nevertheless will be or has also been published. It also has been peer reviewed. It discloses the neuroprotective activity of three additional representative compounds disclosed in the present application in multiple in vitro models of neuronal injury and after controlled cortical impact in mice. In the studies described therein, the compounds were tested over a range of doses in well characterized in vitro models of necrosis and apoptosis, as well as in a mouse model of controlled cortical impact TBI. Further, the authors examined whether treatment effects might be mediated through changes in the expression patterns for endogenous neurotoxic and/or neuroprotective factors, after injury, using high density oligonucleotide micro arrays. Further, in vitro calcium imaging was used to examine whether the neuroprotective actions of the compounds were associated with reduced changes for the cation.

As shown therein, these three additional compounds showed that they reduced cell death after direct physical trauma or trophic withdrawal. Representative compounds also protected against glutamate toxicity and β-amyloid – induced injury, both of which are well established

models to test the ability of a drug to effect neuroprotection. Representative compounds also strongly inhibited glutamate – induced increases in intracellular calcium. As shown, treatment with each of the test compounds resulted in highly significant improvement of motor and cognitive recovery after CCI, and exhibited marked reduced lesion volumes, as shown by high field magnetic resononic imaging. DNA microarray studies following fluid percussion induced traumatic brain injury (TBI) in rats showed that treatment with representative compounds of the present invention after injury significantly down regulated expression of mRNA's for cell cycle proteins, aquaporins, cathepsins and calpain in ipsilateral cortex and/or hippocampus, while up-regulating expression of brain derived neurotrophic factor, hypoxia-inducible factor and several heat – shock proteins.

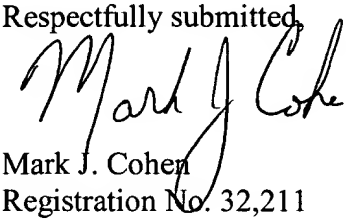
Thus, the data presented to date provides, inter alia, evidence that representative compounds of the present invention provide neuroprotection from stroke, brain injury and spinal cord injury.

At the interview, Examiner Gupta indicated that based on the evidence to date, the specification is enabling for the neuroprotection resulting from stroke, brain injury and spinal cord injury.

Accordingly, for the reasons provided, the rejection of Claims 12-17, 21, 22, and 73-77 under 35 USC § 112, first paragraph is overcome; withdrawal thereof is respectfully requested.

Thus, in view of the comments hereinabove, and the Amendment to the Claims, it is respectfully submitted the present case is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,



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